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17. (Amended) The composition of claim 16 wherein the active drug is a alfaxalone.

## REMARKS

Reconsideration of this application is requested. Claims 1-20 remain active in the application subsequent to entry of this Amendment. The claims have been amended in order to more particularly point out and distinctly claim the disclosed invention.

In revised claims 1 and 2, "autoclavable" is derived in context from page 1, paragraph 3, line 2-4 of the specification, "The preferred method of sterilization of pharmaceutical parenteral agents is terminal sterilization by autoclaving. It has been found that many surface modified submicron- to micron-sized particle suspensions undergo particle size growth during autoclaving."

In revised claims 1 and 2, "non-flocculating" is derived in context from page 3, paragraph 6, lines 1-3 of the specification, "These compositions did not use any surfactants that would require cloud point modifying molecules for protection against coagulation, flocculation, crystal growth, or particle size growth during the terminal steam sterilization process." Protection against flocculation is a critical feature of the current invention. Formulations that flocculate during or after autoclaving are not desired and are excluded from the invention as illustrated in Example 2 and in Table II which present the results of some negative control experiments wherein flocculation is an undesired outcome. The use of the term "non-flocculating" is further supported in the abstract of the current invention:

> "Compositions of submicron- to micron-sized particles of water-insoluble biologically active substances that are stabilized by thermoprotecting agents, can be terminally steam sterilized without any significant increase of mean particle size. **These compositions display markedly reduced heat-induced coagulation, flocculation, or particle size growth during the terminal steam sterilization process.**"

The qualifying descriptor "phospholipid" applied to "surface modifier" in claims 1, 2, 7, 8, 9, and 10 clarifies the inventive concept and further defines the scope of the claimed invention. Applicant's claims are intended to be directed only to those autoclavable, non-flocculating aqueous suspension compositions that are stabilized with at least one phospholipid surface modifier as hereinabove described.

In claim 5, suitable osmotic pressure is qualified by inserting the phrase from claim 4 "for safe parenteral administration" that was omitted in the original submission.

**Response to Art-Based Rejection**

The examiner states that "Muller et al (5,858,410 or '410) anticipate Claims 1 to 20 of 121-176 because '410 teach a drug carrier composition 0.001–30% lecithin (Claims 1, 13, 15), the compounds glucose, mannose, trehalose or sorbitol (Claims 1, 19, 22), and 0.1-30% active (Claims 1, 7). Parenteral, intramuscular and subcutaneous administration (Col. 8, line 61, col. 9 line 33). Antimycotic, corticoid, and immuno therapeutics such as cyclosporin are specified (claims 39, 48)."

The following are Claims 1, 19, 20, 21 and 22 in the disclosure of '410 (emphasis added).

1. "Drug ***carrier*** comprising particles of at least one therapeutically active compound which is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents, wherein said active ingredient is solid at room temperature and has an average diameter, determined by photon correlation spectroscopy (PCS) of 10 nm to 1,000 nm, the proportion of particles larger than 5 .mu.m in the total population being less than 0.1% (number distribution determined with a Coulter counter), and, when introduced into water, aqueous media and/or organic solvents, the active compound has an increased saturation solubility and an increased rate of dissolution compared with powders of the active compound prepared using an ultrasonic probe, a ball mill or a pearl mill, the solid particles having been comminuted, without prior conversion into a melt, by using a piston-gap homogenizer."

19. "***Carrier*** according to claim 1, further ***comprising one or more viscosity-increasing substances***."

20. "***Carrier*** according to claim 19, further comprising ***viscosity-increasing substances in an amount of 0.1 to 20 wt.%, based on the total weight of said carrier***."

21. "Carrier according to claim 19 wherein the ***viscosity-increasing substances comprises cellulose ethers and esters, polyvinyl alcohol, alginates, xanthans, pectins, polyacrylates, poloxamers and poloxamines***."

22. "Carrier according to claim 19, further ***comprising a compound selected from the group consisting of sugars or sugar alcohols, glucose, mannose, trehalose, mannitol and sorbitol***."

Further '410 *(Col. 7, lines 21-29)* discloses that studies

"have been carried out on the sterilizability by autoclaving and also by means of gamma sterilization. The influence of the following parameters on sterilizability was determined:
a. the chemical nature of the surfactant (e.g. lecithins, various phospholipids and, as ethoxylated stabilizers, Tween 80 and Pluronic)
b. mixtures of two or more surfactants
c. the concentration of the surfactants or stabilizers."

Based on these studies '410 discloses *(Col. 7, line 30)* "on the basis of theoretical considerations" that *(Col. 7, lines 63-65)* "surfactant concentrations in the range from one to several per cent are therefore employed." Also, the disclosure of '410 then goes on to teach that however *(Col. 8, lines 19-26)* "sterilization of nanosuspensions stabilized with a varying surfactant concentration surprisingly resulted in the lowest particle growth at a Tween 80 concentration of 0.03% to 0.1%, that is to say in the range of the concentration for reaching the plateau of the adsorption isotherms or also slightly below this (example 12). ***This means that at very low surfactant and stabilizer concentrations, nanosuspensions are optimum starting suspensions for autoclaving.***" However, in Example 10 of the disclosure of '410 *(col. 15, lines 52-62)* referring to the same set of experiments as in Example 12 Muller et al disclose Example 10, "The number of particles greater than 5 μm rose as a result of exposure of the nanosuspensions to heat and the resulting formation of aggregates. In nanosuspension A 1+2, diluted with 2 parts of water, the number of particles >5 μm increased above the value of the more highly concentrated, non-sterilized parent suspension A, but still remained significantly below the values of the fat emulsions. ***Dilution with 9 parts of water lowered the probability of***

***collision of two particles due to the reduction in the particle concentration so greatly that a significant increase in the number of particles before and after sterilization was no longer detectable.***" Thus in addition to low surfactant concentrations a low active concentration is also critical to successful sterilization.

In the disclosure of '410, claims 19, 20, 21, 22 of '410 relate to "***viscosity-increasing substances***" that include "***sugars or sugar alcohols, glucose, mannose, trehalose, mannitol and sorbitol.***" Further, '410 discloses that the role of the viscosity-increasing agents is ***"to reduce sedimentation during pumping through the homogenizer"*** and that the "***particle size obtained during dispersion is a function*** of the power density employed, the hardness of the drug, ***the viscosity of the dispersion medium*** (increase in the power density with the viscosity at a constant flow rate of the dispersing phase) and the surfactant properties." Further in Example 10 of the disclosure, Muller et al conclude that the presence of the viscosity modifier (16.7% mannitol) has no effect on sterilizability of preparations of the drug. This applies to both steam (heat) as well as gamma (radiation) sterilization.

In summary, the disclosure of '410 in relation to the current application teaches the use of dilute preparations of active and low surfactant concentrations as being necessary for steam and gamma sterilization.

The disclosure of '410 makes no specific teaching on conditions for the steam sterilization of phospholipid containing nanosuspensions or the need for any non-surfactant polyhdroxy compound that acts as a thermoprotectant. Muller et al in '410 refer (in Column 7, line 65 to Column 8, line 1) to "the standard surfactant concentrations

in O/W emulsions for parenteral feeding is therefore also 1.2% lecithin (e.g. commercial products such as Intralipid, Lipofundin, Endolipide, Lipovenos etc.)." Muller et al consider this concentration range for to be too high to be useful for stabilization of their suspensions by surfactants during sterilization. Rather, Muller et al teach that use of decreasingly smaller amounts of surfactant provides better stability to suspensions on autoclaving (see '410, column 8, lines 19-26). In the limit, they prepare "surfactant-free" nanosuspensions (column 8, lines 28-29). In their list of possible applications (column 9, lines 43), Muller et al teach that a pulminary administration form includes "instillation of the dispersion, where substances which promote spreading, such as phospholipids or phospholipid-associated proteins, **are possibly added**" (i.e., the presence of phospholipids is not a requirement).

Muller et al in '410 disclose an example of the "stability of nanosuspensions during sterilization: autoclaving A121" in Example 10 (column 15) with reference to Figure 13 and 14. The nanosuspension formulations examined do not contain phospholipids. Rather, comparison is measured against phospholipid-containing Lipofundin 10%, an emulsion with a relatively large number of particles greater than 5 micrometers per mL which was not autoclaved by Muller et al and which is also outside of the scope of the current invention. Muller et al in their example 10 of '410 disclose that diluting a parent suspension of "3% RMKP 22, 0.3% Tween 80, 16.7% mannitol, *aqua dest.* add to 100 wt.%" with 2 parts of water provided a suspension of particles that grew more in size that after sterilization at 121°C for 15 minutes than a suspension produced by dilution with 9 parts of water after sterilization. They conclude that

"dilution with 9 parts of water lowered the probability of collision of two particles due to the reduction in the particle concentration so greatly that a significant increase in the number of particles before and after sterilization was no longer detectable." Muller et al thus teach that the surfactant concentration should be decreased to achieve better particle stability. This conclusion was confirmed in their Example 12 with reference to Figure 17. Their observation are given in column 16, lines 62-67: "The nanosuspension with 1% Tween 80 already showed macroscopic visible aggregates after autoclaving, and was therefore no longer analysed by means of the laser diffractometer. Surprisingly, the nanosuspensions showed a higher stability with decreasing surfactant concentration."

The current application teaches away from the disclosure of '410. Specifically, revised Claim 1 requires an "autoclavable, non-flocculating aqueous suspension composition of a water insoluble or poorly soluble biologically active substance together with at least one phospholipid surface modifier and a pharmaceutically acceptable, water soluble polyhdroxy thermoprotecting agent, wherein the ratio of active substance to surface modifier and thermoprotecting agent is selected to provide particle size stability during and after terminal steam sterilization, and wherein a change in volume weighted particle size is not more than a two-fold increase subsequent to terminal steam sterilization." Further, applicant teaches (Description of the Invention, para 7) that the thermoprotecting agents have a role distinct from the surfactants (or surface modifying agents); viz, "While the surface modifiers possibly adsorb to the freshly made surfaces of drug particles during the process of particle size reduction, and (a) convert lipophilic drug surface to hydrophilic surface that has increased stability, and (b) possibly modify the

surface charge of the drug particle surfaces, the thermoprotecting agent and thermoprotecting conditions described herein help maintain the particle size distribution of the suspension during and after the terminal steam sterilization conditions." Applicant also specifies thermoprotecting conditions (Claim 2) "wherein the composition is substantially completely devoid of surfactants that require elevation of their cloud point temperature by addition of a cloud point modifier for further stabilization and substantially devoid of surfactant additives which cause destabilization of the formulation."

In summary, unlike Muller et al in their disclosure of '410, the current application teaches the use of non-surfactant polyhdroxy thermoprotectants and other thermoprotecting conditions that allow the steam sterilization autoclaving of phospholipid containing nanosuspensions and phospholipid containing microparticle preparations of water-insoluble drugs. As shown in the Example, the invention can be used for the sterilization of very high drug concentrations. The current application also identifies a broad composition range and conditions wherein certain "ratios" of components are required. It also identifies certain agents to be excluded to allow steam sterilization. These are in contrast to the need for dilution for successful sterilization taught in the '410 citation. The ability to sterilize high concentrations of active material is highly desirable from a market and end-user perspective.

Independent of '410 applicant and his collaborators have conducted experiments that demonstrate Tween-80 containing compositions of other phospholipid stabilized

nanosuspensions of other drugs are not steam sterilizable. For example, a preparation of the following composition (% w/w) was made and sterilized:

Cyclosporine 5.0%
Trehalose 12.0%
Lipoid E80 2.0%
Tween 80 0.2%
Water, DI QS to 100%
pH adjusted to 6.6

A premix of the above composition was homogenized for about 100 passes through an Avestin C5 homogenizer at 18000-20000 psi with the fluid temperature at the inlet of the homogenizer maintained at about 13°C. The particle size of the final homogenized product was measured with a Malvern Mastersizer. This product displayed a monomodal distribution with a volume weighted mean diameter of 1.12 μm and 100 percentile below 2.46μm. Upon steam sterilization at 121°C for 15 minutes the suspension displayed sedimentation which could be resuspended by gentle agitation. However, the particle size increased to a volume weighted mean of 10.85μm with the 100 percentile as high as 22.5μm.

It should be noted that the quantity of Tween 80 used in this study was very small (only 0.2% w/w) and according to '410 the suspension should not have suffered from the effects demonstrated by the high percentage of Tween 80 in the formulation as mentioned by Muller et al in the '410 patent. Thus, the presence of Tween-80, even at a small concentration was sufficient to destabilize the formulation particle size during the autoclaving step. In this respect, Tween-80 as a surface modifier is a destabilizer for the

cyclosporine formulation and not the stabilizer as Muller has found for the compound RMKP-22. The effect of Tween-80 as a stabilizer mentioned by Muller may be limited only to RMKP-22 and cannot be generalized.

**Response to Claim Indefiniteness Rejection**

The term "suitable" has been removed from claims 4 and 5 as being implicit and replaced with "acceptable" where appropriate. The first occurrence of the term "suitable" in claim 5 as originally worded refers and thus restricts and limits the term to the finite number of well known diluents that can be used for injection ("*parenteral administration*") and not to a diluent of any other quality that cannot be injected. The second occurrence of the term "suitable" in claim 5 refers to an osmotic pressure range that is commonly practiced for injectable preparations, *e.g.*, an osmotic pressure range isotonic with blood. Claim 4 also contains the word "suitable" and again the intent is to specify an osmotic pressure acceptable for parenteral administration.

For the above reasons, it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and favorable allowance are solicited.

Respectfully submitted,

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# APPENDIX OF CLAIMS

1. (Amended) An autoclavable, non-flocculating aqueous suspension composition of a water insoluble or poorly soluble biologically active substance together with at least one phospholipid surface modifier and a pharmaceutically acceptable, water soluble polyhdroxy thermoprotecting agent, wherein the ratio of active substance to surface modifier and thermoprotecting agent is selected to provide particle size stability during and after terminal steam sterilization, [provided that the] and wherein a change in volume weighted particle size is not more than a[n about] two-fold increase [in the volume weighted mean particle size of the particulate aqueous suspension] subsequent to terminal steam sterilization.

2. (Amended) An autoclavable, non-flocculating aqueous suspension composition of a water insoluble or poorly soluble biologically active substance together with at least one phospholipid surface modifier and a pharmaceutically acceptable, water soluble polyhdroxy thermoprotecting agent, wherein the ratio of active substance to surface modifier and thermoprotecting agent is selected to provide particle size stability during and after terminal steam sterilization, [provided that the] wherein a change in volume weighted particle size is not more than a[n about] two-fold increase [in the volume weighted mean particle size of the particulate aqueous suspension] subsequent to terminal steam sterilization, and wherein the composition is substantially completely devoid of surfactants that require elevation of their cloud point temperature by addition of a cloud

point modifier for further stabilization and substantially devoid of surfactant additives which cause destabilization of the formulation.

3. (Amended) The composition of claim 1 wherein the pH of the suspension before terminal steam sterilization is between about 5 to about 9 provided the pH value prior to terminal steam sterilization is selected such that the chemical stability of the suspension components is maintained during and after [the] terminal steam sterilization [step].

4. (Amended) The composition of claim 1 wherein the composition also includes an amount of non-surfactant additives such that the composition attains [a suitable]an osmotic pressure acceptable for safe parenteral administration.

5. (Amended) The composition of claim 1 wherein the composition also includes an amount of non-surfactant additive such that, on diluting the formulation with pharmaceutically acceptable diluent [suitable] for parenteral administration to a pharmaceutically acceptable concentration for parenteral administration, [a suitable] osmotic pressure acceptable for safe parenteral administration of the diluted suspension results.

7. (Amended) The composition of claim 1 wherein [one or more of] the phospholipid surface modifier[s are] is selected from the group consisting of natural phospholipids [or] and synthetic phospholipids.

8. (Amended) The composition of claim 7 wherein the natural phospholipid [surface_modifier] is an egg phospholipid or soy phospholipid.

9. (Amended) The composition of claim 1 wherein the amount of the phospholipid surface modifier provides a drug to surface modifier ratio of up to 5:1.

10. (Amended) The composition of claim 1 wherein the amount of phospholipid surface modifier is in the range from about 0.2% w/w to about 5.0% w/w.

12. (Amended) The composition of claim 1 wherein the active substance is an antifungal agent.

15. (Amended) The composition of claim 14 wherein the active substance is a cyclosporin.

16. (Amended) The composition of claim 1 wherein the active drug is a sterol.

17. (Amended) The composition of claim 16 wherein the active drug is a alfaxalone.